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PATENT

Applicant	:	Gopal	)	Group Art Unit: 1636 #23
Reissue Appl.	:	09/404,979	)	
Filed	:	September 22, 1999	)	
For	:	PEPTIDE-MEDIATED GENE TRANSFER	)	
Examiner	:	McKelvey, T.	)	

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DECLARATION OF PATRICIA A. JENNINGS, PH.D.

I, Patricia A. Jennings, Ph.D., do hereby declare:

1. I am a citizen of the United States of America residing at 5447 Dalen Ave., San Diego, CA 92122.

2. I received my Ph.D. in Chemistry in 1991 from Pennsylvania State University, University Park, PA. I am currently an Associate Professor, University of California, San Diego, Dept. of Chemistry & Biochemistry. A true and correct copy of my curriculum vitae is attached.

3. I have extensive educational and research experience in the experimental analysis of protein and peptide structure and mechanisms of peptide folding.

4. I have been retained by Genetic Applications, the assignee of the above-identified application. I have no ownership interest in the application. Genetic Applications is paying me the normal hourly rate charged by me for my consulting services in this area of my expertise.

5. I understand that the above-identified application is a reissue application of U.S. Patent No. 5,670,347, filed as application Serial No. ("SN") 240,514 on May 11, 1994 ("the Gopal patent"), and that the application has an effective filing date of May 11, 1994.

6. I have reviewed the above-identified application, together with the presently pending claims. As I understand it, the subject matter claimed in the application is directed to a transfection vector comprising a synthetic polypeptide linked electrostatically to a DNA structural sequence, wherein the polypeptide comprises (A) a polymeric chain of basic amino acid residues, (B) a nuclear localization signal (NLS) peptide and (C) a hinge region of neutral amino acids that connects the polymeric chain and the NLS peptide.

7. I am aware of the discussions between the Examiner and the Applicant with regard to U.S. Patent No. 5,994,109 to Woo et al. ("the '109 patent") during prosecution of the above-identified application. In essence, the Applicant was able to overcome any potential rejection over the '109 patent by distinguishing the inventive "hinge region" of the above-identified application from the "spacer" employed in the '109 patent. This is evidenced by an Examiner Interview Summary Record dated December 19, 2000, an Examiner Interview Summary Record dated January 22, 2001, and the fact that the Examiner allowed the application.

8. I understand that Woo et al. obtained additional patents related to the '109 patent, including U.S. Patent No. 6,150,168 ("the '168 patent"). I understand that the '168 patent, which like the '109 patent, is a divisional of application SN 08/167,641, has the same disclosure as the '109 patent. I also understand that the '168 patent contains claims to "a hinge region," including claims to "a hinge region... comprised of glycine and serine." *See* the '109 patent at claims 36, 37, 39 and 40.

9. I understand that both of the above-mentioned Woo et al. patents stem from application SN 07/855,389, filed March 20, 1992, and that therefore the earliest possible effective filing date is March 20, 1992. I have been retained to attest to the state of the art at this time and at the effective filing date of the Gopal patent.

10. Scientists working in the field of peptide biology prior to 1992 routinely used the terms "spacer" and "hinge" in a highly specific and mutually exclusive manner: (a) spacers have extended structures permitting them to hold attached functional moieties in fixed spatial positions while (b) hinges are flexible regions that allow large movements of one attached moiety relative to another attached moiety.

11. The biophysical properties of spacers permit them to provide a predictable distance between attached moieties. The physical properties of hinges permit them to provide flexibility.

12. A spacer acts as a distance holder between two attached moieties. This biophysical property of a spacer was known by Woo et al., as evidenced by their definition provided at col. 9, lines 4-29, of the '168 patent, wherein Woo et al. provides a laundry list of well-known spacers.

13. The requirement for a spacer to provide a predictable separation distance has been discussed extensively in the literature. Spacer failure, sometimes called "fold back," must be avoided in order to provide the biophysical properties of a spacer. Thus, the art prior to and at the effective filing dates of the Woo et al. patents and the Gopal patent taught the need to avoid the physical property of "folding back" that arises when the spacer fails to provide a predictable separation distance between its bound moieties.

14. While spacers provide a predictable length and separation distance, hinge regions must be depicted dynamically. Hinges allow large movement relative to their tethered domains. Substantial work has been done in characterizing such freedom of movement in polypeptides before the effective filing dates of the Woo et al. patents and the Gopal patent. As shown in the Figure 1, attached hereto, in a hinge, the distance between the rigid arm ends, r, changes as a function of angles β (.beta.) and ψ(.psi.). Note that as the hinge allows changes in the angle β (.beta.) the arm A' rotates through space altering the distance between it and arm A. The distance between A' and A

varies because of the hinge region. This property would preclude our ability to reliably predict the distance between the attached moieties and is thus contrary to the definition of a spacer.

15. The $[(gly)_i(ser)_j]_k$, wherein i=1-6; j=1-6; and k=3-20, spacer disclosed at col. 9, lines 4-29, of the '168 patent is well documented in the literature. Huston's review describes eleven different published uses for $[(gly)_i(ser)_j]_k$ spacers by 1991. (Huston 1991 Table 1, p. 53).

16. The $[(gly)_i(ser)_j]_k$, wherein i=1-6; j=1-6; and k=3-20, spacer has specific biophysical properties due to the periodic placement of hydroxylated (polar) serine residues. The hydrophilic serine can maintain stability and conformation in solution through hydrogen bonding to water or the main chain. (*See* Argos, p. 956). It is this steric hindrance introduced by periodically spaced serine residues hydrogen bonding to water, or the main chain, that prevents "folding back."

17. On the other hand, the Gopal patent teaches the use of "a hinge region of neutral amino acid, to minimize steric interference between the two [attached] domains." (*See, e.g.,* Abstract). A hinge region containing a stretch of glycines is used as an example. (*See* the Gopal patent at col. 10), A stretch of glycines lacks the steric interference of the serine residues that stabilizes the $[(gly)_i(ser)_j]_k$, wherein i=1-6; j=1-6; and k=3-20, spacer.

18. The length of glycine hinges can vary considerably, as shown in the National Center for Biotechnology Information (NCBI) database, sponsored by the National Institutes of Health (NIH). For example, splicing factor SC35 (SFR2_HUMAN), contains a glycine hinge with four consecutive glycine residues: GGGGYG. (Accession #Q01130, entered Apr 1, 1993). Whereas Seed Chitinase A (CHIA_MAIZE), contains a glycine hinge with fourteen consecutive glycine residues: GGGGGGGGGGGGGSGG. (Accession #P29022, entered Dec. 1, 1992).

19. The polypeptide spacer taught by the Woo et al. patents, *i.e.*, $[(gly)_i(ser)_j]_k$, wherein i ranges from 1 to 6; j ranges from 1 to 6; and k ranges from 3 to 20, is not a "hinge region comprised of glycine and serine." The use of 3 to 20 regularly spaced serine residues provides steric

interference through hydrogen bonding to water or the main chain. (*See* Argos, p. 956). Thus, the peptide formula in the Woo et al. patents is "conformationally stable." *Id.*

20. Interestingly, Huston continued to improve on his original ($[(gly)_4(ser)_1]_y$) spacer. In WO 92/15682, Huston improved fidelity and stability by decreasing the percentage of glycine in his spacer $[(ser)_4(gly)_1]_y$, wherein $y>1$. (*See* pp. 3 and 24).

21. Based on my analysis above, I find that the structures identified as spacers in the Woo et al. patents are less flexible than a hinge region such as that containing a stretch of glycines and are therefore unable to perform the novel function of the hinge region disclosed in the Gopal patent and the instant application. It would be clear to those reading the examples of the spacers in the Woo et al. patents and the examples of hinge regions in the Gopal patent (and the instant application) that these two structures have distinct biophysical properties and that one does not suggest the use of the other.

22. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or patent issuing therefrom.

Respectfully submitted,

Dated: 8/29/02 By: Patricia A Jennings

Patricia A. Jennings, Ph.D.

Exhibits:

Exhibit 1 – Curriculum Vitae

Exhibit 2 – U.S. Patent No. 5,670,347

Exhibit 3 – U.S. Patent No. 5,994,109

Exhibit 4 – U.S. Patent No. 6,150,168

Exhibit 5 – Figure 1

Exhibit 6 – Argos, et al., J. Mol. Biol., 211: 943-958 (1990).

Exhibit 7 – WO 92/15682

Exhibit 8 – Accession No. Q01130 (1993).

Exhibit 9 – Accession No. P29022 (1992).